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Help

Logout

Interrupt

Main Menu

Search Form

Posting Counts

Show S Numbers

Edit S Numbers

Preferences

Cases

Search Results -

Term	Documents
ASTHMA.DWPI,EPAB,JPAB,USPT,PGPB.	30228
ASTHMAS.DWPI,EPAB,JPAB,USPT,PGPB.	99
(1 AND ASTHMA).USPT,PGPB,JPAB,EPAB,DWPI.	38
(L1 AND ASTHMA).USPT,PGPB,JPAB,EPAB,DWPI.	38

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US Pre-Grant Publication Full-Text Database
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Derwent World Patents Index

Database:

IBM Technical Disclosure Bulletins

Search:

L2

Refine Search

Recall Text

Clear

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DATE: Sunday, July 21, 2002 [Printable Copy](#) [Create Case](#)

Set Name Query
side by side

Hit Count Set Name
result set

DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ

L2 L1 and asthma38 L2L1 fibronectin same (alternatively adj spliced)94 L1

END OF SEARCH HISTORY

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Print

L2: Entry 23 of 38

File: USPT

DOCUMENT-IDENTIFIER: US 6117840 A

TITLE: CS-1 peptidomimetics, compositions and methods of using the same

Brief Summary Text (19):

More specifically, these in vivo studies are as follows: contact hypersensitivity (CH) and delayed type hypersensitivity (DTH) in the mouse and rat [Ferguson et al., Proc. Natl. Acad. Sci. USA, 88:8072-8076 (1991); Issekutz, Cell Immunol., 138:300-312 (1991); Issekutz, J. Immunol., 147:4178-4184 (1991); Elices et al., Clin. Exp. Rheumatol., 11:S77-80 (1993); Chisholm, et al., Eur. J. Immunol., 23:682-688 (1993)]; experimental autoimmune encephalomyelitis (EAE) in the mouse and rat [Yednock et al., Nature, 356:63-66 (1992); Baron et al., J. Exp. Med., 177:57-68 (1993)]; nephrotoxic nephritis in the rat [Mulligan et al., J. Clin. Invest., 91:577-587 (1993)]; passive cutaneous anaphylaxis in the guinea pig [Weg et al., J. Exp. Med., 177:561-566 (1993)]; immune complex-induced lung injury in the rat [Mulligan et al., J. Immunol., 150:2401-2406 (1993); Mulligan et al., J. Immunol., 150:2407-2417 (1993)], spontaneous colitis in the monkey [Poldolsky et al., J. Clin. Invest., 92:372-380 (1993)] and asthma in sheep [Lobb, WO 92/13798 published Jul. 22, 1993].

Drawing Description Text (6):

FIG. 4 shown in two panels as FIG. 4A and FIG. 4B illustrates the effects of a contemplated peptide in treating asthma in the rabbit. FIG. 4A shows the percent change in dynamic compliance (C.sub.dyn) over a six-hour time period immediately following the onset of induced asthma attacks. Data for rabbits treated by a nebulized composition containing the inhibitor peptide N--phenylacetyl--Leu--Asp--Phe--morpholinamide are shown as open circles, whereas data for untreated rabbits are shown with darkened circles; both circles including error bars. The ordinate is in units of percent change from the initial dynamic compliance value, whereas the abscissa is in units of hours after challenge.

Detailed Description Text (96):

Particular inflammatory disease states that are mediated by CS1 and VLA4, and in which a contemplated inhibitor peptide can diminish inflammation are quite broad. Illustrative of those types of inflammation are asthma, arthritic conditions such as rheumatoid arthritis and osteoarthritis, allograft rejection, various types of skin inflammation, and demyelinating diseases of the central nervous system.

Detailed Description Text (107):

For example, for the treatment of asthma in rabbits, the dose of a contemplated peptide is in the range of about 1 to 100 mg/day for a 2-3 kg animal. For a human asthma patient, that dose is in the range of about 1 to about 100 mg/day for a 70 kg patient. Administration for asthma is typically by aerosol from a nebulizer. Ideally, therapeutic administration should begin as soon as possible after the attack begins.

Detailed Description Text (115):

Methods for determining an amount sufficient to inhibit binding between CS and VLA4 have already been discussed, particularly for in vitro studies. For in vivo uses, there are many published assays to determine if inflammation has been reduced by a particular treatment. For example, one can assess the number of painful joints in an arthritic patient or the patient's mobility before and after treatment. Reduction of effects of an asthma attack can be assayed by measurement of dynamic compliance or lung resistance in laboratory animals as is also well known. The amount of edema

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Print

L2: Entry 24 of 38

File: USPT

DOCUMENT-IDENTIFIER: US 6087330 A

TITLE: Process to inhibit binding of the integrin .alpha..sub.4 .beta..sub.1 to VCAM-1 or fibronectin and cyclic peptides therefor

Brief Summary Text (10):

For example, some of the diseases that might be treated by the inhibition of .alpha..sub.4 .beta..sub.1 binding include, but are not limited to, atherosclerosis, rheumatoid arthritis, asthma, allergy, multiple sclerosis and type I diabetes. In addition to being found on some white blood cells, .alpha..sub.4 .beta..sub.1 is found on various cancer cells, including leukemia, melanoma, lymphoma and sarcoma cells. It has been suggested that cell adhesion involving .alpha..sub.4 .beta..sub.1 may be involved in the metastasis of certain cancers. Inhibitors of .alpha..sub.4 .beta..sub.1 binding may, therefore, also be useful in the treatment of some forms of cancer.

Brief Summary Text (26):

The adhesion of leukocytes to the vascular endothelium and their subsequent extravasation into tissues are critical steps in the inflammatory response. Vascular cell adhesion molecule-1 (VCAM-1), a member of the immunoglobulin superfamily, is expressed by endothelial cells and a restricted number of other cell types. VCAM-1 can be induced by cytokines such as tumor necrosis factor-.alpha..sub.1, interleukin-4, and interleukin-1.beta. and is therefore hypothesized to contribute to leukocyte extravasation in inflammatory conditions such as rheumatoid arthritis, asthma, and atherosclerosis.

Brief Summary Text (28):

.alpha..sub.4 .beta..sub.1 also recognizes the extracellular matrix glycoprotein fibronectin. Three distinct .alpha..sub.4 .beta..sub.1 -binding sites have been identified within fibronectin and all have been reproduced in synthetic form. One site (represented by the peptide H1) is found in the HepII region and is therefore expressed in all fibronectin isoforms; two others (represented by peptides CS1 and CS5) are present in the alternatively spliced type III connecting segment. Of these three the CS1 peptide has the higher affinity for .alpha..sub.4 .beta..sub.1 and contains the tripeptide Leu-Asp-Val (LDV) as its minimal active site. H1 contains a related motif, Ile-Asp-Ala (IDA), while CS5 incorporates a variant of the prototypic RGD motif, Arg-Glu-Asp-Val.

Brief Summary Text (72):

A process of the present invention is especially useful in treating diseases associated with uncontrolled migration of white blood cells to damaged tissue. Such diseases include, but are not limited to, asthma, atherosclerosis, rheumatoid arthritis, allergy, multiple sclerosis, leukemia, and brain cancer.

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[Help](#)
[Logout](#)
[Interrupt](#)
[Main Menu](#)
[Search Form](#)
[Posting Counts](#)
[Show S Numbers](#)
[Edit S Numbers](#)
[Preferences](#)
[Cases](#)

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[Refine Search](#)
[Recall Text](#)
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 DATE: Sunday, July 21, 2002 [Printable Copy](#) [Create Case](#)

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L2 L1 and asthma

 38 L2
L1 fibronectin same (alternatively adj spliced)

 94 L1

END OF SEARCH HISTORY

observed in DTH is also readily measurable, as are the effects of allograft rejection or its absence compared to standard controls.

Other Reference Publication (4):

Komoriya et al., "The minimal essential sequence for a major cell type-specific adhesion site (CS1) within the alternatively spliced type III connecting segment domain of fibronectin is leucine-asparic acid-valine," J. Biol. Chem. 266:15075-15079 (1991).

CLAIMS:

31. The method according to claim 29 or 30, wherein said inflammation is due to asthma.